

**WHAT IS CLAIMED IS:**

- 1                   1.       A method for modulating the plasma circulation half-life of an active  
2   agent, said method comprising:  
3                   (a) providing a liposome having free active agent and precipitated active agent  
4   encapsulated therein; and  
5                   (b) varying the amount of said active agent that is precipitated in said  
6   liposome.
- 1                   2.       The method of claim 1, wherein step (b) comprises varying said active  
2   agent to lipid ratio.
- 1                   3.       The method of claim 2, wherein said active agent to lipid ratio is varied  
2   by the addition of an empty liposome.
- 1                   4.       The method of claim 1, wherein step (b) comprises varying the size of  
2   said liposome.
- 1                   5.       The method of claim 1, wherein step (b) comprises adding a  
2   component that enhances precipitation of said active agent.
- 1                   6.       The method of claim 5, wherein said component is a mono-, di-, tri-, or  
2   polyvalent anion.
- 1                   7.       The method of claim 1, wherein step (b) comprises varying both said  
2   active agent to lipid ratio and the size of the liposome.
- 1                   8.       The method of claim 1, wherein said active agent is an antineoplastic  
2   drug.
- 1                   9.       The method of claim 8, wherein said antineoplastic drug is a  
2   camptothecin.
- 1                   10.      The method of claim 9, wherein said camptothecin is a member  
2   selected from the group consisting of irinotecan, topotecan, 9-amino camptothecin, 10,11-  
3   methylenedioxy camptothecin, 9-nitro camptothecin, TAS 103, 7-(4-methyl-piperazino-  
4   methylene)-10, 11-ethylenedioxy-20(S)-camptothecin and 7-(2-N-isopropylamino)ethyl)-  
5   20(S)-camptothecin.

- 1 11. The method of claim 10, wherein said camptothecin is topotecan.
- 1 12. The method of claim 1, wherein said active antineoplastic drug is a  
2 vinca alkaloid.
- 1 13. The method of claim 12, wherein said vinca alkaloid is a member  
2 selected from the group consisting of vincristine, vinblastine, vinorelbine and vindesine.
- 1 14. The method of claim 1, wherein the precipitated active agent  
2 encapsulated in said liposome is at least 50% of said total active agent.
- 1 15. The method of claim 14, wherein the precipitated active agent  
2 encapsulated in said liposome is at least 60% of said total active agent.
- 1 16. The method of claim 15, wherein the precipitated active agent  
2 encapsulated in said liposome is at least 70% of said total active agent.
- 1 17. The method of claim 1, wherein said liposome comprises  
2 sphingomyelin and cholesterol.
- 1 18. The method of claim 17, wherein said liposome comprises  
2 sphingomyelin and cholesterol in a 55:45 ratio.
- 1 19. The method of claim 1, wherein the plasma circulation half-life of said  
2 active agent is modulated for optimum efficacy.
- 1 20. The method of claim 1, wherein the ratio of said active agent to lipid is  
2 about 0.005-1:1 (w/w).
- 1 21. The method of claim 20, wherein the ratio of said active agent to lipid  
2 is about 0.05-0.9:1 (w/w).
- 1 22. The method of claim 21, wherein the ratio of said active agent to lipid  
2 is about 0.1-0.5:1 (w/w).
- 1 23. A method for modulating the plasma circulation half-life of an active  
2 agent, said method comprising:

3 (a) providing a liposome having free active agent and precipitated active agent  
4 encapsulated therein; and

5 (b) adding a liposome with no encapsulated active agent.

1 24. The method of claim 23, wherein the ratio of liposomes containing  
2 active agent to liposomes with no encapsulated agent is from about 1:0.5 to 1:1000.

1 25. The method of claim 24, wherein the ratio of liposomes containing  
2 active agent to liposomes with no encapsulated agent is from about 1:1 to 1:100.

1 26. The method of claim 25, wherein the ratio of liposomes containing  
2 active agent to liposomes with no encapsulated agent is from about 1:2 to 1:10.

1 27. The method of claim 26, wherein the ratio of liposomes containing  
2 active agent to liposomes with no encapsulated agent is from about 1:3 to 1:5.

1 28. The method of claim 23, wherein said active agent is an antineoplastic  
2 drug.

1 29. The method of claim 28, wherein said antineoplastic drug is a  
2 camptothecin.

1 30. The method of claim 29, wherein said camptothecin is a member  
2 selected from the group consisting of irinotecan, topotecan, 9-amino camptothecin, 10,11-  
3 methylenedioxy camptothecin, 9-nitro camptothecin, TAS 103, 7-(4-methyl-piperazino-  
4 methylene)-10, 11-ethylenedioxy-20(S)-camptothecin and 7-(2-N-isopropylamino)ethyl)-  
5 20(S)-camptothecin.

1 31. The method of claim 30, wherein said camptothecin is topotecan.

1 32. A liposomal formulation, said liposomal formulation comprising:  
2 a) an antineoplastic drug; and  
3 b) a liposome having free antineoplastic drug and precipitated  
4 antineoplastic drug, wherein the precipitated antineoplastic drug in said liposome is at least  
5 50% of the total antineoplastic drug.

1 33. The liposomal formulation of claim 32, wherein said antineoplastic  
2 drug is a camptothecin.

1                   34.    The liposomal formulation of claim 33, wherein said camptothecin is a  
2    member selected from the group consisting of irinotecan, topotecan, 9-amino camptothecin,  
3    10,11-methylenedioxy camptothecin, 9-nitro camptothecin, TAS 103, 7-(4-methyl-  
4    piperazino-methylene)-10, 11-ethylenedioxy-20(S)-camptothecin and 7-(2-N-  
5    isopropylamino)ethyl)-20(S)-camptothecin.

1                   35.    The liposomal formulation of claim 34, wherein said camptothecin is  
2    topotecan.

1                   36.    The liposomal formulation of claim 33, wherein said antineoplastic  
2    drug is a vinca alkaloid.

1                   37.    The liposomal formulation of claim 32, wherein the free antineoplastic  
2    drug and the precipitated antineoplastic drug are different.

1                   38.    The liposomal formulation of claim 36, wherein said vinca alkaloid is a  
2    member selected from the group consisting of vincristine, vinblastine, vinorelbine and  
3    vindesine.

1                   39.    The liposomal formulation of claim 32, wherein the ratio of said  
2    antineoplastic drug to lipid is about 0.005-1:1 (w/w).

1                   40.    The liposomal formulation of claim 39, wherein the ratio of said  
2    antineoplastic drug: said lipid is about 0.05-0.9:1 (w/w).

1                   41.    The liposomal formulation of claim 40, wherein the ratio of said  
2    antineoplastic drug: said lipid is about 0.1-0.5:1 (w/w).

1                   42.    The liposomal formulation of claim 32, wherein said liposome  
2    comprises sphingomyelin and cholesterol.

1                   43.    The liposomal formulation of claim 42, wherein said liposome  
2    comprises sphingomyelin and cholesterol in a 55:45 ratio.

1                   44.    The liposomal formulation of claim 32, further comprising a liposome  
2    with no encapsulated active agent.

1                   45.     The liposomal formulation of claim 44, wherein the ratio of liposomes  
2 containing active agent to liposomes with no encapsulated agent is from about 1:0.5 to  
3 1:1000.

1                   46.     The liposomal formulation of claim 45, wherein the ratio of liposomes  
2 containing active agent to liposomes with no encapsulated agent is from about 1:1 to 1:100.

1                   47.     The liposomal formulation of claim 46, wherein the ratio of liposomes  
2 containing active agent to liposomes with no encapsulated agent is from about 1:2 to 1:10.

1                   48.     The liposomal formulation of claim 47, wherein the ratio of liposomes  
2 containing active agent to liposomes with no encapsulated agent is from about 1:3 to 1:5.

1                   49.     A liposomal formulation, said liposomal formulation comprising:  
2 a) an active agent;  
3 b) a liposome having free active agent and precipitated active agent  
4 encapsulated therein; and  
5 c) an empty liposome.

1                   50.     The liposomal formulation of claim 49, wherein the ratio of liposomes  
2 containing said active agent to said empty liposomes is from about 1:0.5 to 1:1000.

1                   51.     The liposomal formulation of claim 50, wherein the ratio of liposomes  
2 containing said active agent to said empty liposomes is from about 1:1 to 1:100.

1                   52.     The liposomal formulation of claim 51, wherein the ratio of liposomes  
2 containing said active agent to said empty liposomes is from about 1:2 to 1:10.

1                   53.     The liposomal formulation of claim 52, wherein the ratio of liposomes  
2 containing said active agent to said empty liposomes is from about 1:3 to 1:5.

1                   54.     The liposomal formulation of claim 49, wherein said active agent is an  
2 antineoplastic drug.

1                   55.     The liposomal formulation of claim 54, wherein said antineoplastic  
2 drug is a camptothecin.

1                   **56.**     The liposomal formulation of claim **55**, wherein said camptothecin is a  
2 member selected from the group consisting of irinotecan, topotecan, 9-amino camptothecin,  
3 10,11-methylenedioxy camptothecin, 9-nitro camptothecin, TAS 103, 7-(4-methyl-  
4 piperazino-methylene)-10, 11-ethylenedioxy-20(S)-camptothecin and 7-(2-N-  
5 isopropylamino)ethyl)-20(S)-camptothecin.

1                   **57.**     The liposomal formulation of claim **56**, wherein said camptothecin is  
2 topotecan.

1                   **58.**     The liposomal formulation of claim **57**, wherein said antineoplastic  
2 drug is a vinca alkaloid.

1                   **59.**     The liposomal formulation of claim **58**, wherein said vinca alkaloid is a  
2 member selected from the group consisting of vincristine, vinblastine, vinorelbine and  
3 vindesine.

1                   **60.**     The liposomal formulation of claim **49**, wherein the ratio of said active  
2 agent to lipid is about 0.005-1:1 (w/w).

1                   **61.**     The liposomal formulation of claim **60**, wherein the ratio of said active  
2 agent to lipid is about 0.05-0.9:1 (w/w).

1                   **62.**     The liposomal formulation of claim **61**, wherein the ratio of said active  
2 agent to lipid is about 0.1-0.5:1 (w/w).

1                   **63.**     The liposomal formulation of claim **49**, wherein said liposome  
2 comprises sphingomyelin and cholesterol.